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RESEARCH ARTICLE

NOVEL APPROACHES FOR DEVELOPING NEW ANTIBIOTICS

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ABSTRACT

Antibiotics are an essential part of modern medicine. The creation of antibiotic-resistant mutations among bacteria appears to be unavoidable, and after a few decades, the antibiotic's potency will be reduced, and the antibiotic will be phased out of general use.
The usual approach to dealing with this issue has been to release new antibiotics that kill resistant mutants.
Antibiotics such as penicillin, erythromycin, and methicillin are used to treat infectious infections, however these antibiotics are becoming less efficient as bacteria develop more resistant to them.
Natural products are microorganism, plant, and animal metabolites.
These natural compounds have been used to make lead molecules, which have been used to make a variety of synthetic medications.
Actinomycetes can create a wide range of bioactive compounds, which have been used to treat a number of human infections. Teixobactin was discovered using a new method of culturing bacteria in soil from "a grassy field in Maine." It is active against gram-positive bacteria this review article focuses on different sources of new antibiotics.
Bacteriophages have been found to be antibacterial in animals and could be useful in the treatment of some infectious disorders.
Another option is to develop new antibiotics that target non-multiplying bacteria, which could lead to medications that limit the emergence of antibiotic resistance and improve patient compliance by reducing antibiotic therapy duration.
With one exception, these new discovery techniques have resulted in medicines that are in preclinical research but have not yet entered clinical trials.
For the time being, the bulk of novel antibiotics on the market will most likely be structural mimics of existing antibiotic families or new compounds, both natural and non-natural, that are evaluated against live growing bacteria in the traditional fashion.

KEYWORDS: Reverse Technology, Nurse, Care, Hospital.

INTRODUCTION

World human population is increasing with an alarming rate, and a variety of new types of health issues are raising up.1 Antibiotics are an essential part of modern medicine. The emergence of antibiotic-resistant mutants among bacteria is increasing within a few decades and results in decreased efficacy and withdrawal of the antibiotic from widespread usage. The increase in number of drug-resistant bacteria is a cause of concern. To tackle the growing problem of antibiotic resistance, the research on new antibiotics and other microbial natural products is

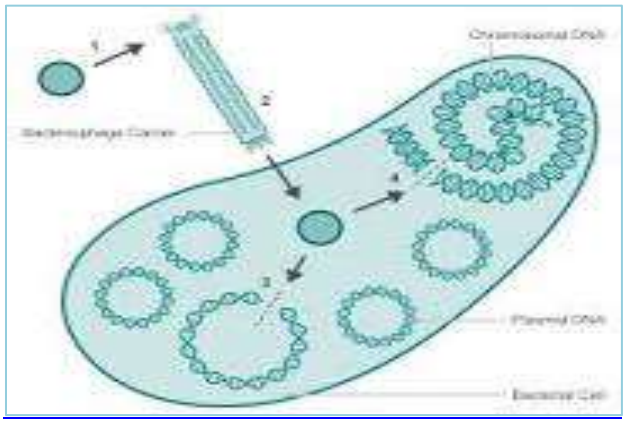
important.1 For the treatment of infectious diseases some antibiotics like penicillin, erythromycin, and methicillin are used but now these antibiotics become less effective because bacteria have become more resistant to such antibiotics. Actinomycetes are prokaryotes of Gram-positive bacteria provide many important bioactive substances which have found application in combating a variety of human infections. More than 70% of naturally occurring antibiotics have been isolated from different genus of actinomycetes. Endophytes are micro-organisms that are found in many important medicinal plants, weeds, and ornamental and fruit trees from wild and domesticated settings and natural products obtained from endophytic microbes are found to be antimicrobial, antiviral, anticancer, antioxidants, anti-diabetic and immunosuppressant.

The first antibiotic, salvarsan, was deployed in 1910. In just over 100 years antibiotics have drastically changed modern medicine and extended the average human lifespan by 23 years. The discovery of penicillin in 1928 started the golden age of natural product antibiotic discovery that peaked in the mid-1950s. Since then, a gradual decline in antibiotic discovery and development and the evolution of drug resistance in many human pathogens has led to the current antimicrobial resistance crisis Here we give an overview of the history of antibiotic discovery, the major classes of antibiotics and where they come from. We argue that the future of antibiotic discovery looks bright as new technologies such as genome mining and editing are deployed to discover new natural products with diverse bioactivities. We also report on the current state of antibiotic development, with 45 drugs currently going through the clinical trials pipeline, including several new classes with novel modes of action that are in phase 3 clinical trials. Overall, there are promising signs for antibiotic discovery, but changes in financial models are required to translate scientific advances into clinically approved antibiotics

BRIEF HISTORY OF RESISTANCE AND ANTIBIOTICS

Penicillin, the first commercialized antibiotic, was discovered in 1928 by Alexander Fleming. Ever since, there has been discovery and acknowledgement of resistance alongside the discovery of new antibiotics. In fact, germs will always look for ways to survive and resist new drugs. More and more, germs are sharing their resistance with one another, making it harder for us to keep up

What is a novel antibiotic?



Scientists have designed a new class of antibiotic which seeks and destroys resistance genes in bacteria. The unique approach could be used to genetically engineer bacteria in our bodies to become less dangerous.

Why do we need new antibiotics?

The discovery of the first antibiotic, penicillin, over 90 years ago, has revolutionised modern medicine. Since then, antibiotics have become one of the most common classes of drugs – used to prevent and treat infections, and make possible complex surgeries that have become routine, from caesarean sections to hip replacement surgeries and organ transplants.

But antibiotics are not as effective as they used to be. Over time certain bacteria, so-called 'superbugs', have adapted and learned to resist the effects of the drugs designed to kill them. Our collective overuse of antibiotics – in humans, animals and plants – has accelerated this process.

Today, drug-resistant infections are a serious threat to people's health. Hundreds of thousands of lives are lost every year because of infections that can no longer be treated with existing drugs. Discovering new antibiotics, able to kill drug-resistant bacteria, is essential to saving modern medicine.

But that's only part of the solution, as over time bacteria will learn to resist the new drugs too. To stay ahead of the game in this constant race against superbugs, we also need innovations in developing vaccines and diagnostics, and better prevention control and surveillance.

Why is it so difficult to develop new antibiotics?

No new classes of antibiotics have been discovered since the 1980s. A class defines a group of antibiotics that have a certain way of working – for example by killing bacteria

or by stopping them multiplying – and are effective against certain types of infections.

The antibiotics that have been brought to market in the past three decades are variations of drugs that have been discovered before.

Discovering and developing genuinely new antibiotics is challenging: the science is tricky and the research and development process is time-consuming and expensive, and often fails.

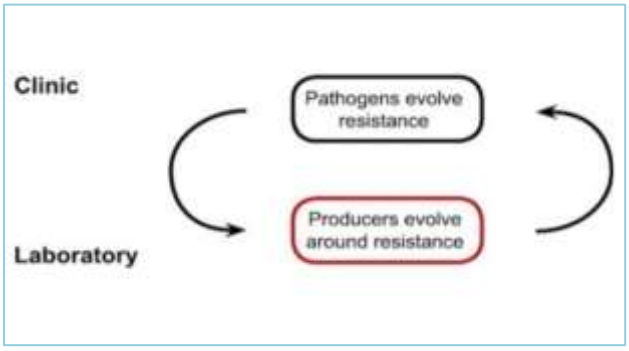
It can take 10-15 years and over $1billion to develop a new antibiotic

How do you know when they will work?

Antibiotics fight bacteria that cause strep throat and ear, sinus and urinary infections. They do not work for the flu, colds, coughs and sore throats. Consult with your doctor about your symptoms, which can help determine the origin of your illness. Ask your doctor about the benefits and drawbacks of taking antibiotics for your diagnosis.

Antibiotics are used to treat bacterial infections. Some are highly specialised and are only effective against certain bacteria. Others, known as broad-spectrum antibiotics, attack a wide range of bacteria, including ones that are beneficial to us.

There are two main ways in which antibiotics target bacteria. They either prevent the reproduction of bacteria, or they kill the bacteria, for example by stopping the mechanism responsible for building their cell walls.



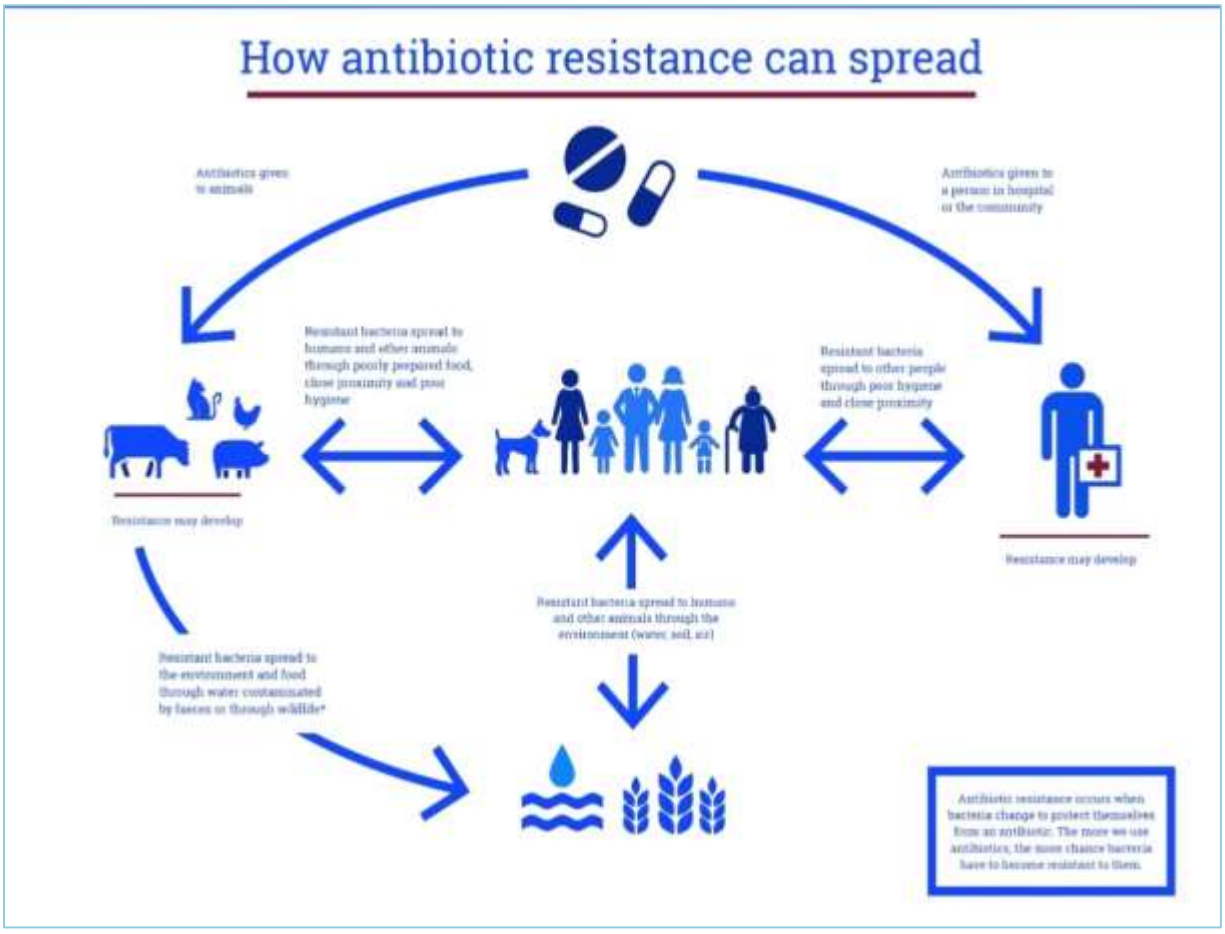


FIGURE 3- Different sources of new antibiotics

ENDOPHYTIC BACTERIA

Endophytes are micro-organisms that are found in many important medicinal plants, weeds, and ornamental and fruit trees from wild and domesticated settings. Both endophytic bacteria and endophytic fungi can co-exist in a single host plant. The natural products obtained from endophytic microbes are found to be antimicrobial, antiviral, anticancer, antioxidants, anti-diabetic and immunosuppressant. Natural products are metabolites from micro-organisms, plants and animals. These natural products have served as sources of lead molecules, which yielded many synthetic drugs. An outstanding example of a natural product is the world's first billion-dollar anticancer-drug, paclitaxel (Taxol) is from Yew tree, Taxus wallachiana. Some examples of the novel antibiotics produced by endophytic bacteria are Ecomycins, Pseudomycins, Munumbicins, Kakadumycins.

Bacteriophages

Bacteriophages and their fragments are also used to kill the bacteria. By an estimate in every 2 days, half of the world's bacterial population is destroyed by bacteriophages. Now in the former Soviet Union bacteriophages are used to treat patients with infectious diseases .In 2006, the FDA approved the use of bacteriophages in the treatment of Listeria monocytogenes contamination of meat and poultry. The development of phage gene products is another potential route for new anti bacterials. Phage lysins, which are cell wall hydrolases and are produced late in the viral infection cycle, bind to peptidoglycan and disrupt the cell wall of Gram-positive bacteria that results in hypotonic lysis. lysins may be active against non-multiplying bacteria and biofilms and this could help in the treatment of catheter-associated infections.

Bacillus species

Bacillus sps isolated from soil exhibited antibacterial activity against bacteria. The study was conducted by ahmed et al in which soil sample from the Post Graduate Hostel of the Permanent Site campus, University of Ilorin, Nigeria was screened for antibiotic-producing microorganisms by agar sensitivity assay. Seven bacterial species were isolated. The bacterial species were identified by their cellular characteristics, colonial morphology and biochemical tests. The bacterial isolates include; Staphylococcus aureus, Proteus vulgaris, Bacillus spp., Pseudomonas aeruginosa, Micrococcus luteus, Escherichia coli and Micrococcus varians. Of all the screened isolates Bacillus spp. was the only bacterial isolate that demonstrated antibiotic producing ability against the tested organisms, showing zones of inhibition around the colonies of two other tested bacteria. Bacillus sps shows antibacterial activity against Escherichia coli and Staphylococcus aureus.

Teixobactin

Teixobactin was discovered using a new method of culturing bacteria in soil from "a grassy field in Maine." It is active against gram-positive bacteria. Teixobactin is an inhibitor of cell wall synthesis that acts primarily by binding to lipid II, a fatty molecule which is a precursor to peptidoglycan. Lipid II is also targeted by the antibiotic vancomycin. Binding of teixobactin to lipid precursors inhibits production of the peptidoglycan layer, leading to lysis of vulnerable bacteria. Teixobactin was reported to be potent in vitro against all gram-positive bacteria tested, including Staphylococcus aureus and difficult-to-treat enterococci, with Clostridium difficile and Bacillus anthracis being exceptionally vulnerable. It also killed Mycobacterium tuberculosis.

Bacteria from soils

Actinomycetes: Actinomycetes are widely distributed in natural and man-made environments and they are found in large numbers in soils, fresh waters, lake, river bottoms, manures, composts and dust as well as on plant residues and food products. Actinomycetes have ability to produce a variety of bioactive substances which has been utilized in a comprehensive series of researches in numerous institutional and industrial laboratories. Thus there are certain agents isolated from them, which have found application in combating a variety of human infections. More than 70% of naturally occurring antibiotics have been isolated from different genus of actinomycetes. Streptomyces is the largest genus known for the production of many secondary metabolites which have different biological activities, such as antibacterial, antifungal, antiparasitic, antitumor, anticancer and immunosuppressive actions

Current methods of antibiotic development

The current methods have concentrated on compounds that target logarithmic multiplying bacteria. For example, natural compounds, such as penicillin, have been discovered by scientific observation, or by searching for such compounds. These natural compounds have provided basic structures such as 6-aminopenicillanic acid, which chemists have used to produce analogues, such as amoxicillin. The analogue route has been very successful for the development of new antibiotics, and continues to be so. Novel compounds were also developed from the non-natural chemical route, for instance, prontosil (the precursor of sulpha drugs), metronidazole, isoniazid and oxazolidinones. Arguably, quinolones may have been created through the non-natural chemical route, although they are originally derived from quinine. Screening of compound collections with enzymes or whole cells, such as target down

regulation by antisense RNA is also used, but have not resulted, as yet, in a marketed antibiotic (see the next section entitled The Genomics Revolution).

Development of new antibiotics

Drug companies are not eager to develop new antibiotics. The process is very costly. To prevent bacteria quickly becoming resistant to the new drugs, doctors will try to use them only as a last resort. So the companies don't expect to get a good return on their investment. The government wants to join forces with other countries to see what incentives could encourage pharmaceutical companies to develop new antibiotics.

SELECTED RESOURCES

Resource	Description
Antibacterial products in clinical and preclinical development: an overview and analysis	Report. A WHO pipeline analysis of antibacterial products targeting the priority pathogens list, Mycobacterium tuberculosis and Clostridium difficile. Includes an assessment of innovativeness. See also the WHO Global Observatory on Health R&D Data and visualizations for the clinical pipeline and preclinical pipeline.
Antibiotics Currently in Global Clinical Development	Document. A pipeline analysis of antibiotics in clinical trials by The Pew Charitable Trusts, provided as a structured list and periodically updated. The data includes systemic antibiotics and drugs for Clostridium difficile.
Global priority list of antibiotic-resistant bacteria to guide research, discovery, and development of new antibiotics	Document. WHO priority pathogens list is the first global effort to guide and promote research and development of new antibiotics. The list comprises 12 bacterial pathogens placed in three priority categories: critical, high and medium (7 pages).
Global AMR R&D Hub's Dynamic Dashboard	Database with information on AMR research and development (R&D) investments, antibacterials in the pipeline and R&D incentives. Note that the information on the investments dashboard does not include data from the pharmaceutical industry.
REVIVE Antimicrobial Encyclopedia	Online encyclopaedia from GARDP. Defines and explains a broad set of terms relating to antibiotics and antibiotic resistance. Focuses particularly on words that are linked to research and development.
From Lab Bench to Bedside: A Backgrounder on Drug Development	Article that gives a simple and brief introduction to the drug-development process.
What is a clinial trial?	Fact sheet. Overview and facts about clinical trials.
Why can't we find new antibiotics?	Video explaining antibiotic discovery and problems related to developing new drugs (2:43 min). Need to click "browse free" for limited access to a few articles

Why so few antibiotics in development?

Here are some of the reasons:

Scientific difficulties: It is extremely difficult to develop an antibiotic drug. First, it needs to get to the right place in the body at a high enough concentration without being toxic to the patient. Then, it also has to enter and stay in

the bacterial cell, which has proven very problematic. Efforts to screen large existing libraries of small molecules have failed to find new antibiotics.

Financial and regulatory hurdles: It is very expensive and often takes ten years or more to develop an antibiotic. Each new formulation needs to go through rigorous testing for activity and patient safety, and only a minority will actually make it through the whole drug-development process. Resistance development can be fast and may hamper usability, which could result in low profits for the developing company. In addition, novel antibiotics would have to be used sparingly to avoid resistance development. Companies have pointed out regulatory requirements to be unclear, which have led to uncertainty of the likelihood of approval of new drugs

Lack of know-how: Poor financial incentives in combination with the technical difficulty to develop new antibiotics have made many pharmaceutical companies scale-down or abandon their antibiotic development programs. This has resulted in a loss of skills and specialized personnel in the field.

Select Germs Showing Resistance Over Time

Antibiotic Approved or Released	Year Released	Resistant Germ Identified	Year Identified
Penicillin	1941	Penicillin-resistant Staphylococcus aureus Penicillin-resistant Streptococcus pneumoniae Penicillinase-producing Neisseria gonorrhoeae	1942 1967 1976
Vancomycin	1958	Plasmid-mediated vancomycin-resistant Enterococcus faecium Vancomycin-resistant Staphylococcus aureus	1988 2002
Amphotericin B	1959	Amphotericin B-resistant Candida auris	2016
Methicillin	1960	Methicillin-resistant Staphylococcus aureus	1960
Extended-spectrum cephalosporins	1980 (Cefotaxime)	Extended-spectrum beta-lactamase-producing Escherichia coli	1983
Azithromycin	1980	Azithromycin-resistant Neisseria gonorrhoeae	2011
Imipenem	1985	Klebsiella pneumoniae carbapenemase (KPC)-producing Klebsiella pneumonia	1996
Ciprofloxacin	1987	Ciprofloxacin-resistant Neisseria gonorrhoeae	2007
Fluconazole	1990 (FDA approved)	Fluconazole-resistant Candida	1988
Caspofungin	2001	Caspofungin-resistant Candida	2004
Daptomycin	2003	Daptomycin-resistant methicillin-resistant Staphylococcus aureus	2004
Ceftazidime-avibactam	2015	Ceftazidime-avibactam-resistant KPC-producing Klebsiella pneumonia	2015

CONCLUSIONS

The need for novel antibiotics is substantial as rates of bacterial resistance rise and the current toolbox of effective antibiotics dwindles. Government agencies are supporting the development of novel antimicrobials with new regulatory pathways, improved guidance, and financial assistance. Leveraging these resources can improve the chances of success for clinical development and eventual approval.

REFERENCES

1. Christina A, Christapher V, Bhore SJ. Endophytic bacteria as a source of novel antibiotics: An overview. Pharmacogn Rev. 2013;7(13):11–16.

2. Coates AR, Hu Y. Novel approaches to developing new antibiotics for bacterial infections. Br J Pharmacol. 2007;152(8):1147–1154.
3. Raja A, Prabakaran P, Gajalakshmi P. Isolation and screening of antibiotic producing psychrophilic actinomycetes and its nature from Rothang hill soil against viridians Streptococcussp. Research Journal of Microbiology. 2010;5(1):44–49.
4. Retinowati W. Identification of Streptomyces sp–MWS1 producing antibacterial compounds. Indonesian Journal of Tropical and Infectious Disease. 2010;1(2):82–85.
5. Khanna M, Solanki R, Lal R. Selective isolation of rare actinomycetes producing novel antimicrobial compounds. Int J Adv Biotech Res. 2011;2(3):357–375.
6. Ting AS, Mah SW, Tee CS. Prevalence of endophytes antagonistic towards Fusarium oxysporum f. sp. cubenserace 4 in various plants. American–Eurasian Journal of Sustainable Agriculture. 2009;3(3):399–406.
7. Walsh TA. Inhibitors of β–glucan synthesis. In: Sutcliffe JA, Georgopapadakou NH, editors. Emerging targets in antibacterial and antifungal chemotherapy. England: Chapman and Hall; 1992. p. 349–373.
8. Wani MC, Taylor HL, Wall ME, et al. Plant antitumor agents. VI. The isolation and structure of taxol, a novel antileukemic and antitumor agent from Taxus brevifolia. J Am Chem Soc. 1971;93(9):2325–2327.
9. Gurung TD, Sherpa C, Agrawal VP, et al. Isolation and characterization of antibacterial actinomycetes from soil samples of Kalapatthar, Mount Everest Region. Nepal Journal of Science and Technology. 2009;10:173–182.
10. Jemimah NSV, Srinivasan M, Devi CS. Novel anticancer compounds from marine actinomycetes. Journal of Pharmacy Research. 2011;4(4):1285–1287.
11. Ahmed, Risikat N, Sani, et al. Soil Screening For Antibiotic–Producing Microrgansms. Advances in Environmental Biology. 2013;7(1):7–11.
12. Grady D. New Antibiotic Stirs Hope Against Resistant Bacteria. The New York Times; 2015.
13. Ling LL, Schneider T, Peoples AJ, et al. A new antibiotic kills pathogens without detectable resistance. Nature. 2015;517(7535):455–459.
14. Hendrix RW. Bacteriophages: evolution of the majority. Theor Popul Biol. 2002;61(4):471–480.
15. Sulakvelidze A, Alavidze Z, Morris JG. Bacteriophage therapy. Antimicrob Agents Chemother. 2001;45(3):649–659.
16. Fischetti VA, Nelson D, Schuch R. Reinventing phage therapy: are the parts greater than the sum? Nat Biotechnol. 2006;24(12):1508–1511.
17. Balaban NQ, Merrin J, Chait R, et al. Bacterial persistence as a phenotypic switch. Science. 2004;305(5690):1622–1625.
18. Akbari, R., Hakemi-Vala, M., Pashaie, F., Bevalian, P., Hashemi, A., and Bagheri, K. P. (2019). Highly synergistic effects of melittin with conventional antibiotics against multidrug-resistant isolates of Acinetobacter baumannii and Pseudomonas aeruginosa. Microb. Drug Resist. 25, 193–202. doi: 10.1089/mdr.2018.0016 PubMed Abstract | CrossRef Full Text | Google Scholar
19. Al-Mawlawi, Z. S., and Obaid, H. H. (2019). Antibacterial activity of synergistic effect of colicin and gold nanoparticles against klebsiella pneumonia. Indian J. Public Heal. Res. Dev. 10:1041. doi: 10.5958/0976-5506.2019.00198.0 CrossRef Full Text | Google Scholar
20. Andersson, D. I., Balaban, N. Q., Baquero, F., Courvalin, P., Glaser, P., Gophna, U., et al. (2020). Antibiotic resistance: turning evolutionary principles into clinical reality. FEMS Microbiol. Rev. 43, 341–361. doi: 10.1093/femsre/fuaa001 PubMed Abstract | CrossRef Full Text | Google Scholar
21. Aoki, W., and Ueda, M. (2013). Characterization of antimicrobial peptides toward the development of novel antibiotics. Pharmaceuticals 6, 1055–1081. doi: 10.3390/ph6081055
22. PubMed Abstract | CrossRef Full Text | Google Scholar
23. Arya, S. S., Sharma, M. M., Das, R. K., Rookes, J., Cahill, D., and Lenka, S. K. (2019). Vanillin mediated green synthesis and application of gold nanoparticles for reversal of antimicrobial resistance in Pseudomonas aeruginosa clinical isolates. Heliyon 5:e02021. doi: 10.1016/j.heliyon.2019.e02021 PubMed Abstract | CrossRef Full Text | Google Scholar
24. Bankier, C., Matharu, R. K., Cheong, Y. K., Ren, G. G., Cloutman-Green, E., and Ciric, L. (2019). Synergistic antibacterial effects of metallic nanoparticle combinations. Sci. Rep. 9:16074. doi: 10.1038/s41598-019-52473-2 PubMed Abstract | CrossRef Full Text | Google Scholar
25. Banoee, M., Seif, S., Nazari, Z. E., Jafari-Fesharaki, P., Shahverdi, H. R., Moballegh, A., et al. (2010). ZnO nanoparticles enhanced antibacterial activity of ciprofloxacin against Staphylococcus aureus and Escherichia coli. J. Biomed. Mater. Res. B Appl. Biomater. 93,

557–561. doi: 10.1002/jbm.b.31615 PubMed Abstract | CrossRef Full Text | Google Scholar

26. Bayramov, D. F., and Neff, J. A. (2017). Beyond conventional antibiotics — New directions for combination products to combat biofilm. Adv. Drug Deliv. Rev. 112, 48–60. doi: 10.1016/j.addr.2016.07.010 PubMed Abstract | CrossRef Full Text | Google Scholar

27. Bhande, R. M., Khobragade, C. N., Mane, R. S., and Bhande, S. (2013). Enhanced synergism of antibiotics with zinc oxide nanoparticles against extended spectrum β-lactamase producers implicated in urinary tract infections. J. Nanoparticle Res. 15:1413. doi: 10.1007/s11051-012-1413-4 CrossRef Full Text | Google Scholar

28. Boparai, J. K., and Sharma, P. K. (2019). Mini review on antimicrobial peptides, sources, mechanism and recent applications. Protein Pept. Lett. 26, 4–16. doi: 10.2174/0929866526666190822165812 PubMed Abstract | CrossRef Full Text | Google Scholar

29. Borthagaray, G., Mondelli, M., Facchin, G., and Torre, M. H. (2018). "Silver-containing nanoparticles in the research of new antimicrobial agents against ESKAPE pathogens," in Inorganic Frameworks as Smart Nanomedicines, ed. A. M. Grumezescu (Norwich, NY: William Andrew), 317–386. doi: 10.1016/b978-0-12-813661-4.00008-0 CrossRef Full Text | Google Scholar

30. Campoccia, D., Montanaro, L., and Arciola, C. R. (2013). A review of the biomaterials technologies for infection-resistant surfaces. Biomaterials 34, 8533–8554. doi: 10.1016/j.biomaterials.2013.07.089 PubMed Abstract | CrossRef Full Text | Google Scholar

31. Cassone, M., and Otvos, L. (2010). Synergy among antibacterial peptides and between peptides and small-molecule antibiotics. Expert Rev. Anti. Infect. Ther. 8, 703–716. doi: 10.1586/eri.10.38 PubMed Abstract | CrossRef Full Text | Google Scholar

32. Chung, P. Y., and Khanum, R. (2017). Antimicrobial peptides as potential anti-biofilm agents against multidrug-resistant bacteria. J. Microbiol. Immunol. Infect. 50, 405–410. doi: 10.1016/j.jmii.2016.12.005 PubMed Abstract | CrossRef Full Text | Google Scholar

33. Das, P., Sengupta, K., Goel, G., and Bhattacharya, S. (2017). Colistin: pharmacology, drug resistance and clinical applications. J. Acad. Clin. Microbiol. 19, 77–85. doi: 10.4103/jacm.jacm_31_17 CrossRef Full Text | Google Scholar

34. De Breij, A., Riool, M., Cordfunke, R. A., Malanovic, N., De Boer, L., Koning, R. I., et al. (2018). The antimicrobial peptide SAAP-148 combats drug-resistant bacteria and biofilms. Sci. Transl. Med. 10:eaan4044. doi: 10.1126/scitranslmed.aan4044 PubMed Abstract | CrossRef Full Text | Google Scholar

35. de Dicastillo, C. L., Patiño, C., Galotto, M. J., Vásquez-Martínez, Y., Torrent, C., Alburquenque, D., et al. (2019). Novel hollow titanium dioxide nanospheres with antimicrobial activity against resistant bacteria. Beilstein J. Nanotechnol. 10, 1716–1725. doi: 10.3762/bjnano.10.167 PubMed Abstract | CrossRef Full Text | Google Scholar

36. de la Fuente-Nunez, C., Torres, M. D., Mojica, F. J., and Lu, T. K. (2017). Next-generation precision antimicrobials: towards personalized treatment of infectious diseases. Curr. Opin. Microbiol. 37, 95–102. doi: 10.1016/j.mib.2017.05.014 PubMed Abstract | CrossRef Full Text | Google Scholar

37. Divyashree, M., Mani, M. K., Reddy, D., Kumavath, R., Ghosh, P., Azevedo, V., et al. (2019). Clinical Applications of Antimicrobial Peptides (AMPs): where do we stand now? Protein Pept. Lett. 27, 120–134. doi: 10.2174/0929866526666190925152957 PubMed Abstract | CrossRef Full Text | Google Scholar

38. Duplantier, A. J., and van Hoek, M. L. (2013). The human cathelicidin antimicrobial peptide LL-37 as a potential treatment for polymicrobial infected wounds. Front. Immunol. 4:143. doi: 10.3389/fimmu.2013.00143 PubMed Abstract | CrossRef Full Text | Google Scholar

39. Dürr, U. H. N., Sudheendra, U. S., and Ramamoorthy, A. (2006). LL-37, the only human member of the cathelicidin family of antimicrobial peptides. Biochim. Biophys. Acta Biomembr. 1758, 1408–1425. doi: 10.1016/j.bbamem.2006.03.030 PubMed Abstract | CrossRef Full Text | Google Scholar

40. Ebejer, J.-P., Charlton, M. H., and Finn, P. W. (2016). Are the physicochemical properties of antibacterial compounds really different from other drugs? J. Cheminform. 8:30. doi: 10.1186/s13321-016-0143-5 PubMed Abstract | CrossRef Full Text | Google Scholar

41. Eckert, R., Brady, K. M., Greenberg, E. P., Qi, F., Yarbrough, D. K., He, J., et al. (2006). Enhancement of antimicrobial activity against Pseudomonas aeruginosa by coadministration of G10KHc and tobramycin. Antimicrob. Agents Chemother. 50, 3833–3838. doi: 10.1128/AAC.00509-06 PubMed Abstract | CrossRef Full Text | Google Scholar

42. El-Sheekh, M. M., and El Kassas, H. Y. (2014). Biosynthesis, characterization and synergistic effect of phytogenic gold nanoparticles by marine

picoeukaryote Picochlorum sp. in combination with antimicrobials. Rend. Lincei. 25, 513–521. doi: 10.1007/s12210-014-0341-x CrossRef Full Text | Google Scholar

43. Escárcega-González, C. E., Garza-Cervantes, J. A., Vázquez-Rodríguez, A., and Morones-Ramírez, J. R. (2018). Bacterial exopolysaccharides as reducing and/or stabilizing agents during synthesis of metal nanoparticles with biomedical applications. Int. J. Polym. Sci. 2018, 1–15. doi: 10.1155/2018/7045852 CrossRef Full Text | Google Scholar

44. Gajdács, M. (2019). The concept of an ideal antibiotic: implications for drug design. Molecules 24:892. doi: 10.3390/molecules24050892 PubMed Abstract | CrossRef Full Text | Google Scholar

45. Garza-Cervantes, J. A., Chávez-Reyes, A., Castillo, E. C., García-Rivas, G., Ortega-Rivera, O. A., Salinas, E., et al. (2017). Synergistic antimicrobial effects of silver/transition-metal combinatorial treatments. Sci. Rep. 7, 1–16. doi: 10.1038/s41598-017-01017-7 PubMed Abstract | CrossRef Full Text | Google Scholar

46. Garza-Cervantes, J. A., Escárcega-González, C. E., Barriga Castro, E. D., Mendiola-Garza, G., Marichal-Cancino, B. A., López-Vázquez, M. A., et al. (2019). Antimicrobial and antibiofilm activity of biopolymer-Ni, Zn nanoparticle biocomposites synthesized using R. mucilaginosa UANL-001L exopolysaccharide as a capping agent. Int. J. Nanomed. 14, 2557–2571. doi: 10.2147/IJN.S196470 PubMed Abstract | CrossRef Full Text | Google Scholar

47. Garza-Cervantes, J. A., Mendiola-Garza, G., de Melo, E. M., Dugmore, T. I. J., Matharu, A. S., and Morones-Ramirez, J. R. (2020a). Antimicrobial activity of a silver-microfibrillated cellulose biocomposite against susceptible and resistant bacteria. Sci. Rep. 10:7281. doi: 10.1038/s41598-020-64127-9 PubMed Abstract | CrossRef Full Text | Google Scholar

48. Garza-Cervantes, J. A., Meza-Bustillos, J. F., Resendiz-Hernandez, H., Suarez-Cantú, I. A., Ortega-Rivera, O. A., Salinas, E., et al. (2020b). Re-sensitizing ampicillin and kanamycin-resistant E. coli and S. aureus using synergistic metal micronutrients-antibiotic combinations. Front. Bioeng. Biotechnol. 8:612. doi: 10.3389/FBIOE.2020.00612PubMed Abstract | CrossRef Full Text | Google Scholar

49. Gelover, S., Gómez, L. A., Reyes, K., and Teresa Leal, M. (2006). A practical demonstration of water disinfection using TiO2 films and sunlight. Water Res. 40, 3274–3280. doi: 10.1016/j.watres.2006.07.006 PubMed Abstract | CrossRef Full Text | Google Scholar

50. Guo, B. L., Han, P., Guo, L. C., Cao, Y. Q., Li, A. D., Kong, J. Z., et al. (2015). The antibacterial activity of Ta-doped ZnO nanoparticles. Nanoscale Res. Lett. 10:336. doi: 10.1186/s11671-015-1047-4 PubMed Abstract | CrossRef Full Text | Google Scholar

51. Gurjar, M., Azim, A., Baronia, A., and Ahmed, A. (2014). Current concepts in combination antibiotic therapy for critically ill patients. Indian J. Crit. Care Med. 18, 310–314. doi: 10.4103/0972-5229.132495 PubMed Abstract | CrossRef Full Text | Google Scholar

52. He, J., Anderson, M. H., Shi, W., and Eckert, R. (2009). Design and activity of a 'dual-targeted' antimicrobial peptide. Int. J. Antimicrob. Agents 33, 532–537. doi: 10.1016/j.ijantimicag.2008.11.013 PubMed Abstract | CrossRef Full Text | Google Scholar

53. Huo, L., Huang, X., Ling, J., Liu, H., and Liu, J. (2017). Selective activities of STAMPs against Streptococcus mutans. Exp. Ther. Med. 15, 1886–1893. doi: 10.3892/etm.2017.5631 PubMed Abstract | CrossRef Full Text | Google Scholar

54. Jackson, N., Czaplewski, L., and Piddock, L. J. V. (2018). Discovery and development of new antibacterial drugs: learning from experience? J. Antimicrob. Chemother. 73, 1452–1459. doi: 10.1093/jac/dky019 PubMed Abstract | CrossRef Full Text | Google Scholar

55. Jesline, A., John, N. P., Narayanan, P. M., Vani, C., and Murugan, S. (2015). Antimicrobial activity of zinc and titanium dioxide nanoparticles against biofilm-producing methicillin-resistant Staphylococcus aureus. Appl. Nanosci. 5, 157–162. doi: 10.1007/s13204-014-0301-x CrossRef Full Text | Google Scholar

56. Kalita, S., Kandimalla, R., Sharma, K. K., Kataki, A. C., Deka, M., and Kotoky, J. (2016). Amoxicillin functionalized gold nanoparticles reverts MRSA resistance. Mater. Sci. Eng. C 61, 720–727. doi: 10.1016/j.msec.2015.12.078 PubMed Abstract | CrossRef Full Text | Google Scholar

57. Khurana, C., Sharma, P., Pandey, O. P., and Chudasama, B. (2016). Synergistic effect of metal nanoparticles on the antimicrobial activities of antibiotics against biorecycling microbes. J. Mater. Sci. Technol. 32, 524–532. doi: 10.1016/j.jmst.2016.02.004 CrossRef Full Text | Google Scholar

58. Koppen, B. C., Mulder, P. P. G., de Boer, L., Riool, M., Drijfhout, J. W., and Zaat, S. A. J. (2019). Synergistic microbicidal effect of cationic

antimicrobial peptides and teicoplanin against planktonic and biofilm-encased Staphylococcus aureus. Int. J. Antimicrob. Agents 53, 143–151. doi: 10.1016/j.ijantimicag.2018.10.002 PubMed Abstract | CrossRef Full Text | Google Scholar

59. Kora, A. J., and Rastogi, L. (2013). Enhancement of antibacterial activity of capped silver nanoparticles in combination with antibiotics, on model gram-negative and gram-positive bacteria. Bioinorg. Chem. Appl. 2013:871097. doi: 10.1155/2013/871097 PubMed Abstract | CrossRef Full Text | Google Scholar

60. Kościuczuk, E. M., Lisowski, P., Jarczak, J., Strzałkowska, N., Jóźwik, A., Horbańczuk, J., et al. (2012). Cathelicidins: family of antimicrobial peptides. A review. Mol. Biol. Rep. 39, 10957–10970. doi: 10.1007/s11033-012-1997-x PubMed Abstract | CrossRef Full Text | Google Scholar.

61. Krause, K. M., Serio, A. W., Kane, T. R., and Connolly, L. E. (2016). Aminoglycosides: an Overview. Cold Spring Harb. Perspect. Med. 6:a027029. doi: 10.1101/cshperspect.a027029 PubMed Abstract | CrossRef Full Text | Google Scholar

62. Kumar, R., Shukla, S. K., Pandey, M., Pandey, A., Pathak, A., and Dikshit, A. (2016). Synthesis and antimicrobial effects of colloidal gold nanoparticles against prevalent waterborne bacterial pathogens. Cogent Chem. 2:1192522. doi: 10.1080/23312009.2016.1192522 CrossRef Full Text | Google Scholar

63. Le, C. F., Fang, C. M., and Sekaran, S. D. (2017). Intracellular targeting mechanisms by antimicrobial peptides. Antimicrob. Agents Chemother. 61:e02340-16. doi: 10.1128/AAC.02340-16 PubMed Abstract | CrossRef Full Text | Google Scholar

64. Lee, B., and Lee, D. G. (2019). Synergistic antibacterial activity of gold nanoparticles caused by apoptosis-like death. J. Appl. Microbiol. 127, 701–712. doi: 10.1111/jam.14357 PubMed Abstract | CrossRef Full Text | Google Scholar

65. Lee, N.-Y., Ko, W.-C., and Hsueh, P.-R. (2019). Nanoparticles in the treatment of infections caused by multidrug-resistant organisms. Front. Pharmacol. 10:1153. doi: 10.3389/fphar.2019.01153 PubMed Abstract | CrossRef Full Text | Google Scholar

66. Lehár, J., Krueger, A. S., Avery, W., Heilbut, A. M., Johansen, L. M., Price, E. R., et al. (2009). Synergistic drug combinations tend to improve therapeutically relevant selectivity. Nat. Biotechnol. 27, 659–666. doi: 10.1038/nbt.1549 PubMed Abstract | CrossRef Full Text | Google Scholar

67. Lei, J., Sun, L., Huang, S., Zhu, C., Li, P., He, J., et al. (2019). The antimicrobial peptides and their potential clinical applications. Am. J. Transl. Res. 11, 3919–3931. Google Scholar

68. Li, J., Koh, J. J., Liu, S., Lakshminarayanan, R., Verma, C. S., and Beuerman, R. W. (2017). Membrane active antimicrobial peptides: translating mechanistic insights to design. Front. Neurosci. 11:73. doi: 10.3389/fnins.2017.00073 PubMed Abstract | CrossRef Full Text | Google Scholar

69. Lopez-Carrizales, M., Velasco, K. I., Castillo, C., Flores, A., Magaña, M., Martinez-Castanon, G. A., et al. (2018). In vitro synergism of silver nanoparticles with antibiotics as an alternative treatment in multiresistant uropathogens. Antibiotics 7:50. doi: 10.3390/antibiotics7020050 PubMed Abstract | CrossRef Full Text | Google Scholar

70. Magiorakos, A. P., Srinivasan, A., Carey, R. B., Carmeli, Y., Falagas, M. E., Giske, C. G., et al. (2012). Multidrug-resistant, extensively drug-resistant and pandrug-resistant bacteria: an international expert proposal for interim standard definitions for acquired resistance. Clin. Microbiol. Infect. 18, 268–281. doi: 10.1111/j.1469-0691.2011.03570.x PubMed Abstract | CrossRef Full Text | Google Scholar

71. Mahlapuu, M., Håkansson, J., Ringstad, L., and Björn, C. (2016). Antimicrobial peptides: an emerging category of therapeutic agents. Front. Cell. Infect. Microbiol. 6:194. doi: 10.3389/fcimb.2016.00194 PubMed Abstract | CrossRef Full Text | Google Scholar

72. Mantravadi, H. B. (2017). Effectivity of titanium oxide based nano particles on E. coli from clinical samples. J. Clin. Diagnostic Res. 11, DC37–DC40. doi: 10.7860/JCDR/2017/25334.10278 PubMed Abstract | CrossRef Full Text | Google Scholar

73. Mao, R., Teng, D., Wang, X., Xi, D., Zhang, Y., Hu, X., et al. (2013). Design, expression, and characterization of a novel targeted plectasin against methicillin-resistant Staphylococcus aureus. Appl. Microbiol. Biotechnol. 97, 3991–4002. doi: 10.1007/s00253-012-4508-z PubMed Abstract | CrossRef Full Text | Google Scholar

74. Marks, L. R., Clementi, E. A., and Hakansson, A. P. (2013). Sensitization of Staphylococcus aureus to methicillin and other antibiotics in vitro and in vivo in the presence of HAMLET. PLoS One 8:e63158. doi: 10.1371/journal.pone.0063158 PubMed Abstract | CrossRef Full Text | Google Scholar

75. Moncla, B. J., Pryke, K., Rohan, L. C., and Graebing, P. W. (2011). Degradation of naturally

occurring and engineered antimicrobial peptides by proteases. Adv. Biosci. Biotechnol. 02, 404–408. doi: 10.4236/abb.2011.26059 PubMed Abstract | CrossRef Full Text | Google Scholar

76. Montelongo-Peralta, L. Z., León-Buitimea, A., Palma-Nicolás, J. P., Gonzalez-Christen, J., and Morones-Ramírez, J. R. (2019). Antibacterial Activity of combinatorial treatments composed of transition-metal/antibiotics against Mycobacterium tuberculosis. Sci. Rep. 9:5471. doi: 10.1038/s41598-019-42049-5 PubMed Abstract | CrossRef Full Text | Google Scholar

77. Morones, J. R., Luis Elechiguerra, J., Camacho, A., Holt, K., Kouri, J. B., Tapia Ramírez, J., et al. (2005). The bactericidal effect of silver nanoparticles. Inst. Phys. Publ. Nanotechnol. Nanotechnol. 16, 2346–2353. doi: 10.1088/0957-4484/16/10/059 CrossRef Full Text | Google Scholar

78. Morones-Ramirez, J. R., Winkler, J. A., Spina, C. S., and Collins, J. J. (2013). Silver enhances antibiotic activity against gram-negative bacteria. Sci. Transl. Med. 5:190ra81. doi: 10.1126/scitranslmed.3006276 PubMed Abstract | CrossRef Full Text | Google Scholar

79. Mulani, M. S., Kamble, E. E., Kumkar, S. N., Tawre, M. S., and Pardesi, K. R. (2019). Emerging strategies to combat ESKAPE pathogens in the era of antimicrobial resistance: a review. Front. Microbiol. 10:539. doi: 10.3389/fmicb.2019.00539 PubMed Abstract | CrossRef Full Text | Google Scholar

80. Murugan, S. (2018). Investigation of the synergistic antibacterial action of copper nanoparticles on certain antibiotics against human pathogens. Int. J. Pharm. Pharm. Sci. 10, 83–86. doi: 10.22159/ijpps.2018v10i10.28069 CrossRef Full Text | Google Scholar

81. Mwangi, J., Hao, X., Lai, R., and Zhang, Z. (2019). Antimicrobial peptides: new hope in the war against multidrug resistance. Zool. Res. 40, 488–505. doi: 10.24272/j.issn.2095-8137.2019.062 PubMed Abstract | CrossRef Full Text | Google Scholar

82. Naqvi, S. Z. H., Kiran, U., Ali, M. I., Jamal, A., Hameed, A., Ahmed, S., et al. (2013). Combined efficacy of biologically synthesized silver nanoparticles and different antibiotics against multidrug-resistant bacteria. Int. J. Nanomed. 8, 3187–3195. doi: 10.2147/IJN.S49284 PubMed Abstract | CrossRef Full Text | Google Scholar

83. Nishanthi, R., Malathi, S., John, P. S., and Palani, P. (2019). Green synthesis and characterization of bioinspired silver, gold and platinum nanoparticles and evaluation of their synergistic antibacterial activity after combining with different classes of antibiotics. Mater. Sci. Eng. C 96, 693–707. doi: 10.1016/j.msec.2018.11.050 PubMed Abstract | CrossRef Full Text | Google Scholar

84. Oka, H., and Ito, Y. (2000). "ANTIBIOTICS | High-Speed Countercurrent Chromatography," in Encyclopedia of Separation Science, eds E. R. Adlard I D. Wilson, C. F. Poole, and M. Cooke (Amsterdam: Elsevier), 2058–2067. doi: 10.1016/b0-12-226770-2/03311-1 CrossRef Full Text | Google Scholar

85. Panácek, A., Smékalová, M., Kilianová, M., Prucek, R., Bogdanová, K., Věcěrová, R., et al. (2016). Strong and nonspecific synergistic antibacterial efficiency of antibiotics combined with silver nanoparticles at very low concentrations showing no cytotoxic effect. Molecules 21:26. doi: 10.3390/molecules21010026 PubMed Abstract | CrossRef Full Text | Google Scholar

86. Pemovska, T., Bigenzahn, J. W., and Superti-Furga, G. (2018). Recent advances in combinatorial drug screening and synergy scoring. Curr. Opin. Pharmacol. 42, 102–110. doi: 10.1016/j.coph.2018.07.008 PubMed Abstract | CrossRef Full Text | Google Scholar

87. Pendleton, J. N., Gorman, S. P., and Gilmore, B. F. (2013). Clinical relevance of the ESKAPE pathogens. Expert Rev. Anti. Infect. Ther. 11, 297–308. doi: 10.1586/eri.13.12 PubMed Abstract | CrossRef Full Text | Google Scholar

88. Perveen, S., Safdar, N., Chaudhry, G. E., and Yasmin, A. (2018). Antibacterial evaluation of silver nanoparticles synthesized from lychee peel: individual versus antibiotic conjugated effects. World J. Microbiol. Biotechnol. 34:118. doi: 10.1007/s11274-018-2500-1 PubMed Abstract | CrossRef Full Text | Google Scholar

89. Pirrone, V., Thakkar, N., Jacobson, J. M., Wigdahl, B., and Krebs, F. C. (2011). Combinatorial approaches to the prevention and treatment of HIV-1 infection. Antimicrob. Agents Chemother. 55, 1831–1842. doi: 10.1128/AAC.00976-10 PubMed Abstract | CrossRef Full Text | Google Scholar

90. Preston, S. L. (2004). The importance of appropriate antimicrobial dosing: pharmacokinetic and pharmacodynamic considerations. Ann. Pharmacother. 38(9 Suppl.), S14–S18. doi: 10.1345/aph.1E218 PubMed Abstract | CrossRef Full Text | Google Scholar

91. Rout, G. K., Shin, H.-S., Gouda, S., Sahoo, S., Das, G., Fraceto, L. F., et al. (2018). Current advances in nanocarriers for biomedical research and their applications. Artif. Cells Nanomed. Biotechnol. 46, 1053–1062. doi: 10.1080/21691401.2018.1478843

PubMed Abstract | CrossRef Full Text | Google Scholar

92. Ruden, S., Rieder, A., Chis Ster, I., Schwartz, T., Mikut, R., and Hilpert, K. (2019). Synergy pattern of short cationic antimicrobial peptides against multidrug-resistant Pseudomonas aeruginosa. Front. Microbiol. 10:2740. doi: 10.3389/fmicb.2019.02740 PubMed Abstract | CrossRef Full Text | Google Scholar

93. Sarma, P., Mahendiratta, S., Prakash, A., and Medhi, B. (2018). Specifically targeted antimicrobial peptides: a new and promising avenue in selective antimicrobial therapy. Indian J. Pharmacol. 50:1. doi: 10.4103/ijp.IJP_218_18 CrossRef Full Text | Google Scholar

94. Selvaraj, R. C. A., Rajendran, M., and Nagaiah, H. P. (2019). Re-potentiation of β-lactam antibiotic by synergistic combination with biogenic copper oxide nanocubes against biofilm forming multidrug-resistant bacteria. Molecules 24:3055. doi: 10.3390/molecules24173055 PubMed Abstract | CrossRef Full Text | Google Scholar

95. Shahverdi, A. R., Fakhimi, A., Shahverdi, H. R., and Minaian, S. (2007). Synthesis and effect of silver nanoparticles on the antibacterial activity of different antibiotics against Staphylococcus aureus and Escherichia coli. Nanomed. Nanotechnol. Biol. Med. 3, 168–171. doi: 10.1016/j.nano.2007.02.001 PubMed Abstract | CrossRef Full Text | Google Scholar

96. Shaikh, S., Nazam, N., Rizvi, S. M. D., Ahmad, K., Baig, M. H., Lee, E. J., et al. (2019). Mechanistic insights into the antimicrobial actions of metallic nanoparticles and their implications for multidrug resistance. Int. J. Mol. Sci. 20:2468. doi: 10.3390/ijms20102468 PubMed Abstract | CrossRef Full Text | Google Scholar

97. Sharma, D., Kanchi, S., and Bisetty, K. (2019). Biogenic synthesis of nanoparticles: a review. Arab. J. Chem. 12, 3576–3600. doi: 10.1016/j.arabjc.2015.11.002 CrossRef Full Text | Google Scholar

98. Si, Z., Lim, H. W., Tay, M. Y. F., Du, Y., Ruan, L., Qiu, H., et al. (2020). A glycosylated cationic block poly(beta-peptide) reverses intrinsic antibiotic resistance in all ESKAPE Gram-negative bacteria. Angew. Chemie Int. Ed. 59, 6819–6826. doi: 10.1002/anie.201914304.